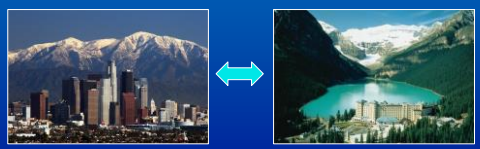
From LA to LL (Lake Louise)
A Clinical Review of HCV Management in the DAA Era



Sammy Saab, MD

Mark Swain, MD

Early/Accurate HCV Diagnosis: Initial Evaluation and Follow-up

History and Physical Examination	Recommended Tests
Risk factors for viral hepatitis Duration of infection Presence of co-morbid disease Complications of liver disease Medications	HCV genotype and viral load Liver function tests Complete metabolic panel Liver biopsy vs elastography vs serum fibrosis tests Tests for other causes of liver diseases Consider HBsAg and HIV testing Hepatitis A immunity If cirrhosis ultrasound, coagulation studies

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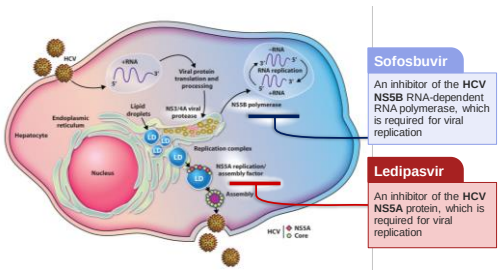
Ledipasvir/Sofosbuvir (Harvoni): Single tablet daily regimen



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Patient Factors in Sofosbuvir/Ledipasvir Therapy for Chronic Hepatitis C Genotype 1

- Sofosbuvir/ledipasvir is approved for the treatment of all adult HCV GT 1 patients
- Patient factors that determine treatment duration include
  - Prior treatment experience
  - Cirrhosis status
  - Baseline viral load
    - For treatment-naïve patients without cirrhosis
- Treatment duration and regimen are *not* impacted by GT 1 subtype (1a vs 1b)

Case Presentations

Case Study I: Role of viral load and fibrosis stage in choosing treatment duration

Patient Profile:

Gender/Age:	Male/46 years
Occupation:	Grocery store owner
Family:	Married with 2 adult children
Height:	5'9"
Weight:	156 lb
BMI:	23

Patient Evaluation:
Laboratory Values

Labs	Values
WBC	4.6
HB	13.2
PLT	280
AST	57
ALT	70
ALB	4.6
TB	0.8

Labs	Values
HCV RNA	1,300,000
HCV Genotype	1a
Fibroscan	8.1 KPa (F2)

Issues

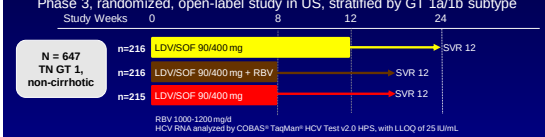
Assessing liver damage

Stability of HCV RNA

Duration of therapy

LDV/SOF±RBV in Treatment-Naïve Non-Cirrhotic GT 1 HCV

Phase 3, randomized, open-label study in US, stratified by GT 1a/1b subtype



- Primary endpoint: SVR 12
- Secondary endpoints: non-inferiority of 8 weeks of LDV/SOF to the other treatment groups
- No upper limit of age or BMI

Demographics

Characteristic	LDV/SOF 8 weeks n = 215	LDV/SOF + RBV 8 weeks n = 216	LDV/SOF 12 weeks n = 216
Mean age, years (range)	53 (22-75)	51 (21-71)	53 (20-71)
Mean BMI, kg/m^2 (range)	28 (18-43)	28 (18-56)	28 (19-45)
Male, n (%)	130 (60)	117 (54)	128 (59)
Race, n (%)			
White	164 (76)	176 (81)	167 (78)
Black	45 (21)	36 (17)	42 (19)
HCV genotype 1a, n (%)	171 (80)	172 (80)	172 (80)
Mean HCV RNA, $\log_{10}$ IU/mL (SD)	6.5 ± 0.76	6.4 ± 0.69	6.4 ± 0.76
HCV RNA < 6 million IU/mL, n (%)	123 (57)	138 (64)	131 (61)
IL28B genotype Non-CC, n (%)	159 (74)	156 (72)	160 (74)
Baseline ALT > 1.5 x ULN	87 (40)	95 (44)	99 (46)
Fibrosis Score (liver biopsy), n (%)	156 (73)	136 (63)	156 (72)
F0-F2	127 (59)	108 (50)	127 (59)
F3	29 (13)	28 (13)	29 (13)
Interferon ineligible, n (%)	13 (6)	13 (6)	15 (7)

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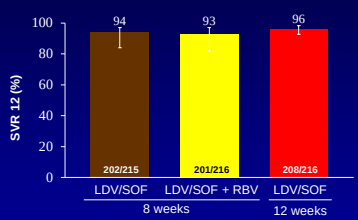
Primary and Secondary Endpoints (ITT Analysis)



	LDV/SOF 8 weeks	LDV/SOF+RBV 8 weeks	LDV/SOF 12 weeks
Relapse Rates	5.1% (11/215)	4.2% (9/216)	1.4% (3/216)

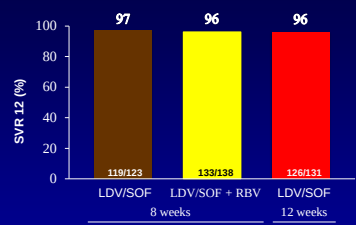
Question 1: The best choice for treating him is:

(a) Harvoni for 12 weeks
(b) Harvoni for 8 weeks
(c) Harvoni + RBV for 8 weeks
(d) Harvoni for 24 weeks

Treating Our Patient

- G1a
- F2 fibrosis (by Fibroscan)
- Baseline Viral Load = 1.3 million IU/ml

Efficacy and Relapse in Subjects with Baseline HCV RNA **< 6 Million** IU/mL



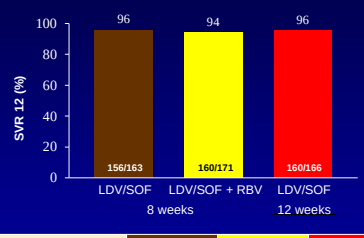
	LDV/SOF 8 weeks	LDV/SOF+RBV 8 weeks	LDV/SOF 12 weeks
Relapse Rates < 6M	1.6% (2/123)	2.2% (3/138)	1.5% (2/131)
Relapse Rates ≥ 6M	9.8% (9/92)	7.8% (6/77)	1.2% (1/85)

Should I change how I treat this man if his baseline viral load was 5.99 million IU/ml??

Question 2: The best choice for treating him now is:

(a) Harvoni for 12 weeks
(b) Harvoni for 8 weeks
(c) Harvoni + RBV for 8 weeks
(d) Harvoni for 24 weeks

Efficacy and Relapse in Subjects with Baseline HCV RNA **≤ 10 Million** IU/mL



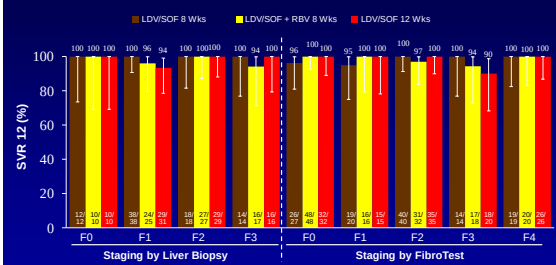
	LDV/SOF 8 weeks	LDV/SOF+RBV 8 weeks	LDV/SOF 12 weeks
Relapse Rates < 10M	3.1% (5/163)	4.1% (7/171)	1.2% (2/166)
Relapse Rates ≥ 10M	11.5% (6/52)	4.4% (2/45)	2.0% (1/50)

Should I change how I treat this man if he had F3 fibrosis??

Question 3: The best choice for treating him now is:

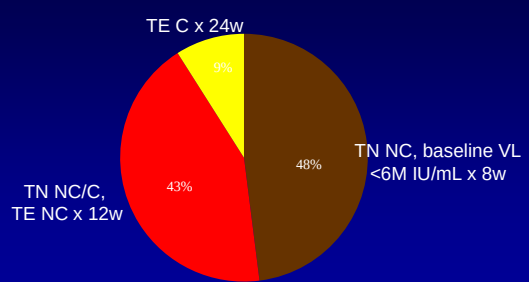
(a) Harvoni for 12 weeks
(b) Harvoni for 8 weeks
(c) Harvoni + RBV for 8 weeks
(d) Harvoni for 24 weeks

SVR12 by Fibrosis Scores Among Patients with Baseline HCV RNA < 6 Million IU/mL



The baseline viral load cut-off of < 6 million IU/mL has high efficacy for all fibrosis stages

Genotype1 Estimated Patient Eligibility for LDV/SOF



C=cirrhotic; M=million; NC=non-cirrhotic; TE=treatment-experienced; TN=treatment-naïve; VL=viral load (HCV RNA); w=week
Source: Ipsos HCV Therapy Monitor (2Q13 to 1Q14)

German Real-World LDV/SOF for 8 Weeks

Single center German study of 45 primarily naïve, non-cirrhotic patients with baseline HCV RNA < 6 million IU/mL treated with LDV/SOF for 8 weeks

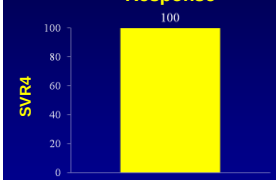
Baseline Characteristics

	N=45
Median (range) age, years	51 (22–73)
Male gender, n (%)	24 (53.3)
Caucasian, n (%)	45 (100)
Genotype, n (%)	
GT 1a/ G1b	22 (48.9) / 21 (46.7)
GT 4	2 (4.4)
Metavir stage, n (%)	
F0	17 (37.8)
F1	15 (33.3)
F2	11 (24.4)
F3	2 (4.4)
Median (range) baseline HCV RNA, IU/mL*	700,259 (5,495–4,677,351)
Treatment-naïve, n (%)†	44 (97.8)
At least one comorbidity, n (%)	39 (86.7)

Buggisch, EASL, 2015, LP32

Effectiveness and Safety

Virologic Response



Safety Results

	Total cohort n=45
Any AEs (Grades 3 & 4), n (%)	1 (2.2)
Headache, n (%)	1 (2.2)
AE related to LDV/SOF, n (%)	1 (2.2)
AE leading to D/C, n (%)	0
Deaths, n (%)	0

*3 patients had no SVR4 data available at time of analysis

LDV/SOF for 8 weeks resulted in high rates of SVR4 and was safe and well tolerated

Buggisch, EASL, 2015, LP32

Case Study II: Impact of being treatment experienced in treatment decisions

Patient Profile

Gender/Age:	Female/48 years
Occupation:	Lab technician
Family:	Married with 1 son
Height:	5'3"
Weight:	125 lb
BMI:	22

Case Study II: Treatment Experienced

Family and Medical History

- Patient has smoked for 10+ years
- Previous relapse after PEG + RBV + BOC therapy (2012)
- Visits to family doctor due to recent fatigue
- Family history of heart disease

Patient Evaluation: *Laboratory Values*

Labs	Values
WBC	3.8
HB	12.8
PLT	110
AST	66
ALT	58
ALB	4.0
TB	1.2

Labs	Values
HCV RNA	7,400,000
HCV Genotype	1a
Fibroscan	12.8 KPa (F4)

Discussion

What additional studies does she need?

Patient Evaluation:
Additional Studies

Study	Results
EGD	Normal
Abdominal ultrasound	Mildly nodular liver

What are the current treatment options for her?

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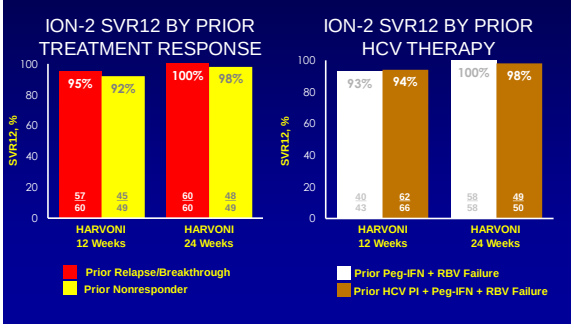
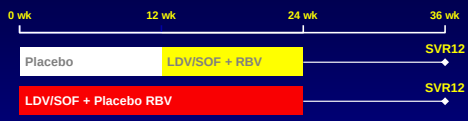
HIGH SVR12 RATES with Harvoni among treatment-experienced subjects REGARDLESS OF PRIOR HCV Therapy



Study Design



- Double-blinded
- Treatment-experienced patients with compensated cirrhosis who did not achieve SVR following sequential PEG + RBV and PI + PEG + RBV regimens
- Stratified
  - HCV genotype (1a, 1b; mixed or other GT 1 results stratified as GT 1a)
  - Prior HCV therapy treatment response (never achieved HCV RNA < LLOQ, achieved HCV RNA < LLOQ)

Demographics

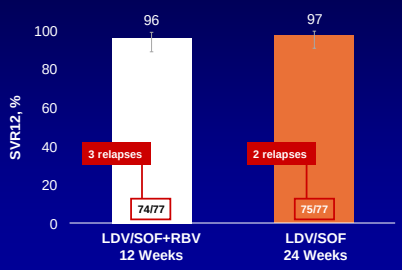
	Placebo 12 Weeks → LDV/SOF+RBV 12 Weeks n=77	LDV/SOF + Placebo RBV 24 Weeks n=78	Total N=155
Mean age, y (range)	56 (39–74)	57 (23–77)	56 (23–77)
Men, n (%)	58 (75)	56 (72)	114 (74)
White, n (%)	76 (99)	75 (96)	151 (97)
Mean BMI, kg/m² (range)	27.9 (19.6–47.1)	26.3 (19.1–39.8)	27.1 (19.1–47.1)
IL28B non-CC, n (%)	73 (95)	72 (92)	145 (94)
Mean MELD (range)	7 (6-16)	7 (6-12)	7 (6-16)
Varices, n (%)	16 (21)	25 (32)	41 (26)
Mean platelets (range)	153 (54–316)	141 (59–278)	147 (54–316)
Platelets <100 x 10^3/µL	14 (18)	13 (17)	27 (17)
Mean albumin, g/dL	3.9 (3.2–4.6)	3.9 (3.0–4.9)	3.9 (3.0–4.9)
Albumin <3.5 g/dL, n (%)	6 (8)	14 (17)	20 (13)
Mean INR (range)	1.1 (0.9–2.4)	1.1 (0.9–1.4)	1.1 (0.9–2.4)
Mean bilirubin mg/dL (range)	0.8 (0.3–2.5)	0.8 (0.3–1.8)	0.8 (0.3–2.5)

Baseline HCV Characteristics

	Placebo 12 Weeks → LDV/SOF+RBV 12 Weeks n=77	LDV/SOF + Placebo RBV 24 Weeks n=78	Total N=155
GT, n (%)			
1a	48 (62)	50 (64)	98 (63)
1b	28 (36)	27 (35)	55 (36)
Mean HCV RNA, $\log_{10}$ IU/mL (range)	6.5 (5.3–7.7)	6.5 (3.9–7.5)	6.5 (3.9–7.7)
Prior PI, n (%)			
Telaprevir	43 (56)	49 (63)	92 (59)
Boceprevir	30 (39)	27 (35)	57 (37)
Other	4 (5)	2 (3)	6 (4)
Baseline NS3/4A RAVs	58 (75)	55 (71)	113 (73)
Previous participation in CUPIC*, n (%)	25 (32)	22 (28)	47 (30)

*CUPIC: ANRS CO20-CUPIC: French cohort of therapeutic failure and resistances in patients treated with a protease inhibitor (telaprevir or boceprevir), pegylated interferon and ribavirin.

Results: SVR12



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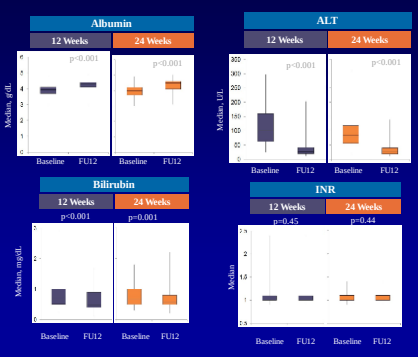
Error bars represent 95% confidence intervals.

Results: Change in Laboratory Parameters



Question 4: The best choice for treating her is:

(a) Harvoni for 12 weeks
(b) Harvoni for 8 weeks
(c) Harvoni + RBV for 12 weeks
(d) Harvoni for 24 weeks

Treating Our Patient

- G1a
- Cirrhotic (by Fibroscan and ultrasound)
- Treatment experienced (with a PI)

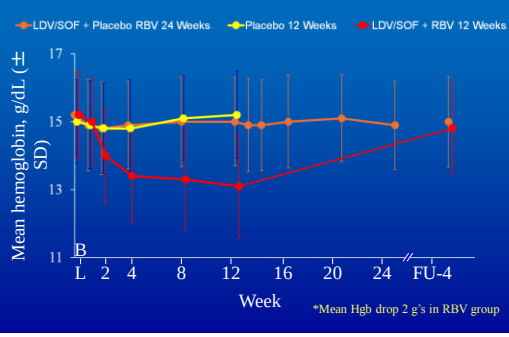
Balancing the Therapeutic Options for Treatment Experienced G1 Cirrhotic Patients

Harvoni + RBV for 12 weeks

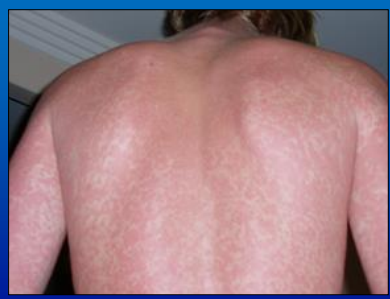
vs

Harvoni alone for 24 weeks

Results: Mean Hemoglobin Over Time

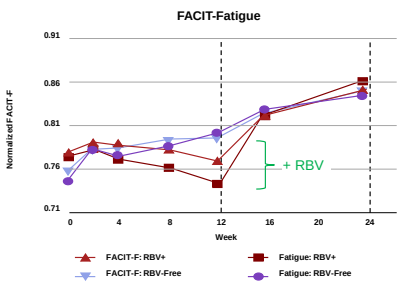


RBV-related Rash



Patients feel better **without** RBV: ‡

LDV/SOF without RBV improves Patient Reported Outcomes (PRO) during treatment course



PRO scores were superior in LDV/SOF (RBV-free) regimens vs. LDV/SOF + RBV regimens after 12 weeks: **Fatigue** (P=0.0006), **Work productivity** (P<0.0001), **Activity impairment** (P=0.0017)

FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue (Younossi Z, EASL, 2014, P1324)

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Results: Safety Summary

	Patients, n (%)	Placebo 12 Weeks → LDV/SOF + RBV 12 Wk			LDV/SOF 24 Wk	
		Placebo 12 Wk n=77	LDV/SOF+RBV 12 Wk n=76	Overall Period n=77	First 12 Wk n=78	Overall Period n=78
Overall Safety	AEs	63 (82)	66 (87)	74 (96)	66 (85)	68 (87)
	Grade 3-4 AEs	1 (1)	5 (7)	6 (8)	2 (3)	10 (13)
	SAEs	1 (1)	3 (4)	4 (5)	3 (4)	8 (10)
	Treatment Related SAEs	0	1 (1)	1 (1)	0	0
	Treatment D/C due to AEs	1 (1)	0	1 (1)	0	0
	Death	0	0	0	0	0
	Grade 3-4 lab abnormalities	18 (23)	8 (11)	24 (31)	15 (19)	11 (14)
	Hb <10 g/dL	1 (1)	1 (1)	2 (3)	0	1 (1)
	Hb <8.5 g/dL	1 (1)	1 (1)	2 (3)	0	0

- Related event was anemia attributed to study treatment
- Treatment D/C due to AEs: bacterial arthritis; decompensated cirrhosis (placebo period)

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Case Study III: Genotype 3

Patient Profile

Gender/Age:	Female/48 years
Occupation:	Disability
Family:	Single
Height:	5'4"
Weight:	125 lb
BMI:	22

Case Study III
Genotype 3

Family and Medical History

- Visits family doctor due to recent fatigue

Patient Evaluation: *Laboratory Values*

Labs	Values
WBC	6.4
HB	12.8
PLT	190
AST	56
ALT	98
ALB	4.0
TB	1.0

Labs	Values
HCV RNA	6,300,000
HCV Genotype	3
Fibroscan	8.2 KPa (F2)

Treatment of Genotype 3 Patients
Sustained Viral Response Rates

Regiment	Non cirrhotic		Cirrhotic		FDA/Health Canada Approved
	Naïve	Experienced	Naïve	Experienced	
SOF/R x 24 weeks	93%	85%	92%	60%	Yes
SOF/LED/R x 12 weeks	100%	89%		73%	No
SOF/PEG/R x 12 weeks		83%		83%	No

Abbreviations: SOF – sofosbuvir; LED – ledipasvir; R-ribavirin; PEG – PegIntereron

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204671s000lbl.pdf
Gane et al
Lawitz et al. Hepatology 2015

Question 5: The best choice for treating this person now is:

(a) Harvoni + RBV for 12 weeks
(b) SOF + RBV for 12 weeks
(c) SOF + RBV for 24 weeks
(d) SOF + PEG + RBV for 12 wks

Treating Our Patient

- G3
- Non-cirrhotic (by Fibroscan)
- Treatment naive

Should I consider changing how I treat this woman if she was treatment experienced and cirrhotic??

Question 6: The best choice for treating this person now is:

(a) Harvoni + RBV for 12 weeks
(b) SOF + RBV for 12 weeks
(c) SOF + RBV for 24 weeks
(d) SOF + PEG + RBV for 12 wks

Treating Our Patient

- G3
- Cirrhotic (by Fibroscan)
- Treatment experienced (PEG + RBV in 2010)

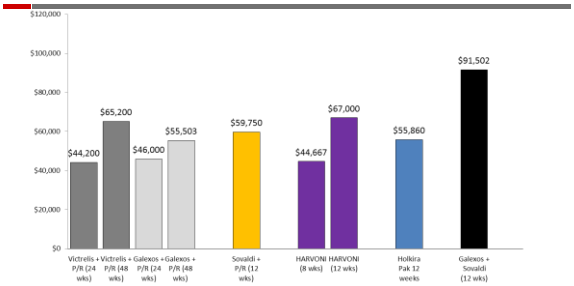
What about daclatasvir??

Genotype 3 Studies Using Daclatasvir

Author	Study	Regiment	Population	Details	SVR
Zeuzem	Valence	S/R x 24 w	Cirrhosis	TN	92%
		S/R x 24 w	Cirrhosis	TE	60%
Kowdley	TRIO	S/R x 24 w	Cirrhosis	TN	73%
			Cirrhosis	TE	57%
Alqahtani	TARGET	S/R x 24	Cirrhosis	TN	92%
		S/R x 24	Cirrhosis	TE	60%
Hezode	French EAP	D/S ± R x 12 w	Advanced cirrhosis	73% TE	76%
		D/ S± R x 24 w	Advanced cirrhosis	73% TE	88%
Foster	English EAP	D/S ± R x 12 w	Decomp cirrhosis	47% TE	70-71%
		H/R x 12 w	Decomp cirrhosis	47% TE	59%
		S/R x 12 w	Decomp cirrhosis	47% TE	43%
Nelson	ALLY-3	D/S x 12 w	Cirrhosis	TN	58%
		D/S x 12 w	Cirrhosis	TE	69%
Poordad	ALLY-1	D/S/R x 12 w	Advanced cirrhosis	60% TE	83%
		D/S/R x 12 w	Post-OLT	58% TE	91%

Questions?

Canadian Regimen Pricing – Direct Acting Antiviral Regimens for the Treatment of Chronic Hepatitis C (Genotype 1)



All prices are in CDN$
P/R = Pegylated-interferon + ribavirin
Source: Prices for Sovaldi, Galexos,, Pegasys RBV and Ibavyr RAMQ Liste de Medicaments October 2014; Victrelis, ODPB e-formulary. HARVONI and Holkira Pak = MLP
Note: Harvoni™ for 24 weeks is recommended for treatment experienced patients with cirrhosis at a regimen cost of $134.00 CDN